REMARKS

Claims 190-194 have each been amended to recite "the DNA or RNA strand," to provide proper antecedent basis.

New claim 202 has been added. New claim 202 recites sequentially identifying by Raman spectroscopy involves analyzing Raman data in which at least one spectral line represents a single nucleotide. Support for this amendment can be found in the specification, for instance, on page 8, lines 28-33. Thus, no new matter has been added.

Claims 188-195 and 198-202 are now pending for examination. Claims 1-17, 19, 23-37, 39, 43-58, 60, 64-72, 74, 78-85, 87, 91-117, 122, 125, 126, 128, 130, 132-135, 138, 139, 146, 147, 153, 155-157, 159-162, 164, 172, 179, 180, 182, 183, 187, 196, and 197 remain withdrawn.

Priority Claim

The Patent Office asserts that U.S. Prov. Apl. Ser. No. 60/076,310, to which the instant application claims priority, does not teach a method for determining a sequence of at least a portion of a DNA or RNA strand comprising the steps recited in the instantly pending claims.

Applicants respectfully disagree. The field of the invention in U.S. Prov. Apl. Ser. No. 60/076,310 states that that application relates to methods for detection of analytes, including sequencing DNA or RNA bases, using SERS. The provisional application teaches that the DNA or RNA fragments can be cleaved with enzymes such as exonucleases or restriction endonucleases known in the art (e.g., page 14, lines 11-13 and 27-28); that surface-enhanced emission spectral information, such as Raman identification, can be used to identify individual DNA or RNA fragments (e.g., page 14, lines 7-11); and that the fragments can each be positioned on a metal film or other surface and identified by identifying their spectral information relative to their locations on the surface (e.g., page 14, lines 24-27).

In addition, the provisional application discloses the use of Raman labels (e.g., page 8, lines 6-7), including labels for various nucleotides (e.g., page 8, lines 5-6), as well as the use of surface enhanced Raman spectroscopy and/or surface enhanced resonance Raman spectroscopy (e.g., page 9, lines 25-28). The provisional application also discloses attaching fragments to a surface, and identifying each fragment on the surface using Raman spectroscopy (e.g., page 14, lines 16-17), including metal films (e.g., page 14, line 10) and metal particles (e.g., page 14, lines 1-3 and page 13, lines 11-14).

Accordingly, for at least these reasons, it is believed that the claims as pending find support in U.S. Prov. Apl. Ser. No. 60/076,310, and it is respectfully requested that priority be properly acknowledged.

Rejections under 35 U.S.C. §112, ¶2

Claims 190-194 have been rejected under 35 U.S.C. §112, ¶2, as failing to point out and distinctly claim the subject matter which the Applicant regards as the invention. The Office Action states that it is unclear when the nucleic acids become labeled.

With respect to the label, it is believed that the claims are definite without specifically reciting a further step of labeling a nucleic acid base (here, thymine, adenine, cytosine, guanine, or uracil, as recited in the claims). These dependent claims merely state that the method involves the use of a DNA or RNA strand comprising a labeled base. It is believed that it is unnecessary to recite exactly when the nucleic acid base becomes labeled, as the claim encompasses embodiments where the labeling of the nucleic acid occurs at any point before, during, or after the steps recited in the claim. Those of ordinary skill in the art would therefore be able to understand what is being claimed, when the claims are read in light of the specification, which is all that is required under 35 U.S.C. §112, ¶2. Accordingly, it is believed that the claims are definite as shown, and it is respectfully requested that the rejection of claims 190-194 be withdrawn.

The Patent Office further rejects claims 190-194 for reciting "the nucleic acids" in the claims. Applicants have corrected this antecedent basis error, and thus respectfully request the rejection be withdrawn.

Rejections under 35 U.S.C. §102(b)

Claims 188-195 and 198-201 have been rejected under 35 U.S.C. §102(b) as being anticipated by Vo-Dinh, U.S. Patent No. 5,306,403 ("Vo-Dinh").

Vo-Dinh does not actually disclose sequencing a DNA or an RNA strand, as is recited in independent claim 188. Vo-Dinh states that "According to the present invention, restriction enzymes, also known as endonucleases, can be selected as the SERS label in certain situations [col. 8, lines 64-66]." Vo-Dinh then describes restriction enzymes in general, and states that "It thus [is] possible to select DNA labels and probes having a SERS-active compound attached to a

specific base pair sequence that can be selectively cleaved by a specific restriction enzyme [col. 9, lines 3-6]." Thus, in Vo-Dinh, the restriction enzyme is used as a SERS label, i.e., a probe having a SERS-active compound is prepared, then attached to a specific base pair sequence that is recognized by the restriction enzyme. The DNA is then cleaved by the restriction enzyme at the specific recognition sequence of four to eight base pairs to release the SERS label from the DNA strand, thereby identifying the DNA strand. Thus, Vo-Dinh does not discuss sequencing the bases of an unknown DNA strand, but rather, Vo-Dinh discloses the identification of a known sequence within a sample, based on a probe that was previously prepared.

Moreover, Vo-Dinh does not disclose or suggest determining the sequence of at least a portion of the DNA or RNA strand based on the sequential identification of each of the one or more fragments by Raman spectroscopy, as is recited in independent claim 188. Restriction enzymes, according to Vo-Dinh, "recognize specific sequences of four to eight base pairs [col. 9, line 2]." Thus, in Vo-Dinh, the restriction enzymes appear to cleave the DNA only into fragments that are defined by restriction sites which are recognized by the restriction enzymes, and those fragments are detected. It is not clear how Raman spectroscopy could then be used in Vo-Dinh to sequence the DNA sequence, as the fragments produced in Vo-Dinh would be at least four base pairs long, and more typically would be tens or hundreds of base pairs long. Vo-Dinh does not teach or suggest how one of ordinary skill in the art could determine the sequences of each of the base pairs comprising each of the DNA fragments produced in this manner using Raman spectroscopy, as one of ordinary skill in the art would not expect to be able to sequence a DNA strand comprising multiple base pairs, but only one SERS-active compound, using Raman spectroscopy. At best, Vo-Dinh refers to L.M. Smith, *et al.*, *Nature*, Vol. 321, p. 674 (1986) and Prober, *et al.*, *Science*, Vol. 238, p. 336 (1987), in reference to Figs. 1 and 2. However, Smith and Prober uses fluorescence, and do not teach or suggest Raman spectroscopy, to sequence DNA fragments (see col. 2, lines 27-61).

Accordingly, it is believed that Vo-Dinh does not anticipate independent claim 188, and it is thus respectfully requested that the rejection of claim 188 be withdrawn. The remaining claims each depend, directly or indirectly, from claim 188, and are believed to be allowable for at least the same reasons. Withdrawal of the rejection of these claims is also respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 188-195, 198, 199 and 201 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dörre, "Techniques for a Single Molecule Sequencing," *Bioimaging*, (Vol. 5, pages 139-152 (1997) ("Dörre") in view of Kneipp, *et al.*, "Single-Molecule Detection Using Surfaced-Enhanced Raman Scattering (SERS)," *Phys. Rev. Lett.*, Vol. 78, No. 9, pages 1667-1670 (1997) ("Kneipp").

To begin, Applicants do not concede that Kneipp is properly prior art to the Applicants' claimed inventions. Applicants believe that they are entitled to the priority date of the provisional application (discussed above), and Applicants reserve the right to establish that Kneipp is unavailable as a reference under §102(a).

Moreover, it is believed that one of ordinary skill in the art would not combine Dörre and Kneipp in the manner suggested in the Office Action. Dörre is directed to sequencing DNA by fluorescent labeling of the DNA, passing the DNA through a microstructured channel, and detecting the DNA using confocal fluorescence microscopy (see, e.g., the abstract), while Kneipp is directed to the detection of single molecules using SERS. Dörre nowhere discloses or suggests to one of ordinary skill in the art to substitute Raman spectroscopy for confocal fluorescence microscopy (indeed, the methodologies and labels for each are quite different), and Kneipp nowhere discloses or suggests the sequencing of nucleic acids such as DNA. The Patent Office has not pointed to an objective teaching, suggestion, or motivation anywhere in Dörre or Kneipp, or anywhere else in the prior art of record, that would lead one of ordinary skill in the art to make the combination of Dörre and Kneipp. Instead, the Patent Office appears to have used hindsight reasoning in making their combination, which is improper.

Absent such an objective motivation to combine Dörre or Kneipp, it is believed that this rejection is improper, and it is thus respectfully requested that the rejection of claims 188-195, 198, 199 and 201 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: July 13, 2006

Respectfully submitted,

By _____

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